REMARKS

The above-identified application has been amended to improve its form. No new matter has been added. Attached hereto is a marked-up version of the changes made to the specification and claims. Favorable action on the application is solicited.

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Respectfully submitted,

By ______________________

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Version With Markings to Show Changes Made

Electrophoresis which makes use of capillaries has been used for the purpose of determining, for example, [such as] base sequencing and base length of DNA. When a specimen containing DNA which is the object of measurement is injected into gel such as polyacrylamide within a glass capillary and a voltage is applied between [the] both ends of the capillary, DNA compounds in the specimen move in the capillary and are separated depending on such as their molecular weights to form DNA bands within the capillary. Since a fluorescent coloring matter is added for the respective DNA bands, when laser beam is irradiated thereto, light is emitted therefrom, thus through reading of the emitted light by means of a fluorescent measurement means the sequencing of DNA is determined. The separation and analysis of protein are performed in [the] a like manner to examine the structure of the protein.

One [of] such laser beam irradiation method[s] is as follows. In a capillary array constituted by a plurality of capillaries, a cover coating such as polyamide on the surface of the capillaries is removed to form a detection portion, laser beam is irradiated to a capillary located at one side or capillaries located at both sides in the detection portion and the laser beam irradiated in such a manner passes across the plurality of capillaries.

(1) An irradiation optical axis making incident in parallel direction with respect to the capillary array plane face is inclined in non-perpendicular direction with respect to the longitudinal direction of the capillaries. Thus, the reflected beam from the capillaries is not overlapped on the laser beam axis, thereby, no noises are introduced.

(3) Incident angles of two laser beam optical axes irradiated from [the] both sides of the capillary plane face which cross each other in parallel direction with respect to the capillary array plane face are differentiated from each other.

When the orthogonal projections of the two incident laser beams with respect to the plane face formed by the capillary array are not [in] parallel as referred to above, the following problem may arise. Since the laser beam diameter when adding the two laser beams becomes large in comparison with when the two laser beams are [in] coaxial, therefore, it is feared that spatial resolution in a fluorescent detection is reduced. Namely, in an electrophoresis, DNA compounds in the specimen move in the capillary and are separated depending on, for example, [such as] their molecular weights to form DNA bands within the capillary. In such an instance, it is possible that the resolution detection capability of these DNA bands is reduced. In order to avoid those possibilities, it is preferable that the centers of the two laser beams overlap[s] each other near the center of the capillary array [each other]. When the two laser beams are arranged like this, the expansion of the laser beam diameter is minimized.

In the above explained method of realizing the laser beam optical axis, the position of the lenses is adjusted so that the laser beams are guided to [a] correct positions of the capillaries. Accordingly, it is preferable that a fine adjustment function for the condenser lenses [are] is provided. With respect to the direction of the laser beam optical axis, when the focal distance of the condenser lenses is 50mm, the positional accuracy of the lenses required for the above direction is about 1mm, therefore, with regard to this direction no positional adjustment function is necessarily required. However, with regard to the two axes perpendicular to the laser beam optical axis, when the ratio of inner diameter/outer diameter of the capillaries is 50µm/3[0]20µm, a positional accuracy of about 10µm is required. In this instance, if a screw having a pitch of about 0.5mm is used as a screw for adjusting the position of the condenser lenses, the requirement will be satisfied.

In the present invention, since the laser beam optical axis is not perpendicular to the capillary axis, when the capillaries are disposed horizontally, the laser beam optical axis can not direct in vertical direction. As a multi-capillary detection means, a two dimensional CCD (Charge Coupled Device) camera is frequently used. In such instance, one

dimension among two dimensions of the CCD camera is aligned along the arrangement direction of the capillaries as an axis for detecting signals from the respective capillaries and the other dimensional axis is aligned along a wave length dispersion direction of fluorescent light emitted from the respective capillaries. Namely, the [later] latter direction is determined as the direction for dispersing the emitted light from the single capillary by making use of [such as] a grating and a prism. In the present invention, although the capillary axis and the laser beam optical axis are not substantially perpendicular, in an electrophoresis apparatus which makes use of a CCD in a fluorescent detection means, it is preferable that a pixel [grating] grid in the CCD is [in] parallel [with] to the optical axis of the laser beam passing through the capillaries rather than [is] substantially [in] parallel [with] to the capillary axis in view of taking-in of data from the CCD.

Further, in an electrophoresis apparatus, including a wave length dispersion means such as a grating and a prism in a fluorescent detection means according to the present invention, it is preferable that the wave length dispersion direction [by] of the wave length dispersion means and the optical axis of the laser beam passing the capillaries are substantially [in parallel] perpendicular to each other in view of taking-in of data from the CCD.

Fig. 12A shows an image [formation] formed on [a] CCDs of a light-emitting substance that is [in a direction in] parallel [with] to grooves in a grating and Fig. 12B is a diagram showing in skeleton of a light intensity distribution of an incident laser beam on a capillary array;

Figs. 3A through 3C show skeleton diagrams near a detection portion of a capillary array and a laser beam introduction route. Since elements such as a shutter and a filter used for laser beam are well known in the field concerned and are not a direct object of the present invention, the illustration thereof is omitted for the sake of simplicity. Fig. 3A is a schematic front view of a major portion of an electrophoresis apparatus according to the present embodiment, Fig. 3B is an upper side view of the detection portion of the capillary array and Fig. 3C is a plane view of a pin hole plate which is attached at an

emission port of a laser beam source. A capillary array is formed by arranging 16 pieces of capillaries 21 on an array stand 20 and by securing the same thereon. Hereinafter, a plane face formed by the center axes of 16 pieces of capillaries 21 on the array stand 20 and an imaginary plane face formed by extending the former plane face over the entire space are called [as] an array face 22. Further, an imaginary straight line which is in the array face is perpendicular to 16 pieces of capillary axes and passes through the center of the detection portion is called [as] a standard optical axis 28 (see Fig. 3A). The capillaries are made of a [quart] quartz glass tube covered by a polymer thin film, however, at the detection portion the polymer covering is removed and the [quart] quartz glass is exposed. The inner diameter/outer [diameter/ outer] diameter ratio of the [quart] quartz glass tube is 50/320μm and the outer diameter of the capillary including the polymer thin film is 363μm. The pitch of the capillaries is 363μm same as the capillary outer diameter and the width of the array is 363μm× 16=5.8mm.

Reflection of the incident laser beam is caused at an interface of air/capillary outer wall and at a capillary inner wall/gel interface. In particular, since a refractive index difference at the interface of air/capillary outer wall is large, the reflection light intensity thereat becomes large. Since there exists two interfaces of air/capillary outer wall for every capillary, reflection is caused from 32 interfaces of air/capillary outer wall of 16 pieces of capillaries.

Fig. 18 shows a signal intensity distribution for the 16 pieces of capillaries in the embodiment 1 above. As will be seen from Fig. 18, when the laser beam is introduced only at one side face of the capillary array, [ratios] variations of signal intensities [from] among the 16 pieces of capillaries are enlarged. According to the present embodiment, the laser beams are introduced from both side faces of the capillary array, thereby, the dispersion of the signal intensities from the 16 pieces of capillaries is reduced.

Fig. 1 shows a skeleton diagram of [the] embodiment 2 according to the present invention, in which only the vicinity of the detection portion of the capillary array and the laser beam introduction route thereof are illustrated and the illustration of the elements

such as a shutter and a filter used for the laser beam is omitted. The structure of the capillary array in [the present invention] embodiment 2 is identical [as] to that in [the] embodiment 1. Further, the name of parts and the definition of terms in the present embodiment are the same as those in [the] embodiment 1 if not otherwise defined. A laser beam 40 is equally divided into two by a half mirror 41 and these two laser beams are irradiated to a capillary array from [the] both side faces thereof. The reflection light by the half mirror 41 is identified as laser beam 43 and the transmitted light is identified as laser beam 44. The condenser lens for the laser beam 43 is identified as a condenser lens 45 and the condenser lens for the laser beam 44 is identified as a condenser lens 46.

A capillary [which positions] positioned at one end of the array and to which the laser beam 43 is first introduced is identified [at] as first capillary 65 hereinbelow and another capillary to which the laser beam 44 is first introduced is identified as 16th capillary 66 hereinbelow. The optical axis layout of the laser beam 43 is the same as that in the embodiment 1. Further, the optical axis layout of the laser beam 44 is in symmetry to that of the laser beam 43 with respect to the capillary array. The optical axes of the laser beams 43 and 44 are adjusted in such a manner that the laser beams 43 and 44 are [in] coaxial and one of the laser beams which passes through the capillaries further passes coaxially through the optical axis of the other incident laser beam and returns to the laser beam source 49. Respective reflection lights 47 and 48 from the capillaries of the laser beams 43 and 44 run in non coaxial manner with respect to the two laser beams 43 and 44 as illustrated in Fig. 1. Like the embodiment 1, at the laser beam emission port of the laser beam source 49 a pin hole plate 51 having a pin hole of a 1.4mm diameter is attached so as to prevent the reflection lights from returning to the laser beam source or the laser oscillator 49. Although the transmitted lights through the capillaries return to the emission port of the laser beam source 49, the returning of the reflection lights to the laser beam source 49 is prevented, thereby, a comparatively stable laser oscillation can be obtained.

Fig. 4A shows a skeleton diagram of a fluorescent detection system according to the present embodiment. An emission light 53 from the capillaries 42 is converted into a

parallel light by an emission light condenser lens 54 of f=1.4[mm] and the parallel emission light is introduced to a transmission type grating 55. Lights 56 and 57 spectrumed by the grating 55 are focused on a two dimension CCD 59 by an image formation lens 58. The wavelength dispersion direction by the grating 55 is substantially perpendicular with respect to the laser beam optical axis. Thereby, among two orthogonally crossing axes on the two dimension CCD 59, one of the axes represents a spatial coordinate in the alignment direction of the 16 pieces of the capillaries and the other axis represents emission light spectrums of the respective capillaries.

[The] L[l]aying out the optical axis according to the present embodiment is realized by making use of a set of the pin hole plates as shown in Fig. 5A. At first, the laser beam condenser lenses 45 and 46 are removed from the electrophoresis apparatus, then pin hole plates 67 and 68 in which pin holes are formed as illustrated in Fig. 5A are disposed at the positions where the laser beam condenser lenses 45 and 46 were disposed. Hereinafter, a crossing line between the pin hole plate and the array face is called as an array reference line 64 and a crossing point of a straight line which is perpendicular to the pin hole plate and passes through the center position of detection portion for the first capillary with the pin hole plate is called [as] a pin hole reference point 69.

Further, [in the present invention,] a reflection light of the incident laser beam which is reflected only once from the surface of the capillaries [makes] is incident [into] on a lens in the fluorescent detection system, and [in the present invention] such direct reflection light is eliminated by an optical filter.

Figs. 9A and 9B show skeleton diagrams of embodiment 3 according to the present invention. Fig. 9A is a front view thereof and Fig. 9B is a side view thereof, in which only the vicinity of the detection portion of the capillary array and the laser beam introduction route thereof are illustrated and the illustration of the elements such as a shutter and a filter used for the laser beam is omitted. In the present embodiment, no incident laser beams run on the array face 22 and the laser beam makes incident with an angle 99 of about 2^0 with respect to the array face 22. The structure of the capillary array

in [the present invention] <u>embodiment 3</u> is identical [as] <u>to</u> that in [the] embodiment 2. Further, the [name] <u>names</u> of parts and the definition of terms in the present embodiment are the same as those in [the] embodiments 1 and 2 if not otherwise defined.

In other words, the above will be explained as follows, when injecting urea aqueous solution of density 8M and refractive index of 1.41 into all of the capillaries and noting a certain specific Raman band [effecting] <u>effected by</u> the incident laser beam 43 as the excitation light source, the position of formed image of the Raman band from the first capillary in the image spectrumed by the grating moves toward a short wavelength in comparison with the position of formed image of the Raman band from the 16th capillary, further, when noting a certain specific Raman band [effecting] <u>effected by</u> the incident laser beam 44 as the excitation light source, the position of formed image of the Raman band from the 16th capillary in the image spectrumed by the grating moves toward a short wavelength in comparison with the position of formed image of the Raman band from the first capillary.

1. (Amended) A capillary array electrophoresis apparatus in which laser beam is irradiated to either one or both end capillaries at both sides of a capillary array constituted by a plurality of capillaries arranged on a plane and the laser beam propagates successively to the adjacent capillary and passes across the plurality of capillaries characterized, in that between a laser oscillator and a laser beam condensing means for condensing the laser beam onto the capillaries an overlapping of reflected laser beam by a capillary face <u>with the incident laser beam</u> is prevented.

5. (Amended) A capillary array electrophoresis apparatus according to claim 4 characterized, in that the capillary array electrophoresis apparatus further comprises a fluorescent detection means using a grating, wherein when a specific liquid having refractive index of 1.41 is injected into all of the capillaries and an image is formed after a certain specific Raman band from the liquid [effecting] <u>effected by</u> the respective opposing two incident laser beams as an excitation light source is spectrumed by the grating, the position of the formed image of the Raman band from the capillary at the laser beam

incident side is shifted toward a short wavelength in comparison with the position of the formed image of the Raman band from the capillary at the laser beam outlet side.

7. (Amended) A capillary array electrophoresis apparatus according to claim [5] 6 characterized, in that the capillary array electrophoresis apparatus further comprises a position adjusting mechanism of [a] the laser beam condenser [lens] lenses.

8. (Amended) A capillary array electrophoresis apparatus according to claim [5] 6 characterized, in that the capillary array electrophoresis apparatus further comprises a laser beam optical axis adjusting jig which is constituted by a set of two plates in each of which two holes having substantially the same diameter as that of the laser beam are formed at positions where the two parallel laser beams pass through.

10. (Amended) A capillary array electrophoresis apparatus according to claim 5 characterized, in that the fluorescent detection means includes a CCD (Charge Coupled Device) camera and pixel grid of the CCD [cameral] camera is substantially [in] parallel [with] to the laser beam optical axis passing the capillaries.